## REMARKS

### I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the commentary below.

### II. Status of the Claims and Specification and Summary of Amendments Thereto

Claims 10, 14, 15, and 17 are currently being amended. Claim 10 is amended to remove the reference to a pharmacologically compatible adjuvant. Claim 14 is amended to correspond with original claim 4. Finally, claim 17 has been redrafted into dependent form to emphasize that claims 10 and 17 share the same special technical features.

Claims 1-9, 11, and 20 were cancelled previously. Claims 10 and 12-19 are therefore pending. Claims 17 and 18 were withdrawn by the PTO.

The specification is amended to incorporate subject matter from the originally filed application. Explicit support for the amendment can be found in original claims 1, 4, and 7.

The amendments eliminate or at least reduce the number of issues in this application. Additionally, the amendments do not introduce new matter. Accordingly, Applicants respectfully request the PTO to enter the amendments.

### III. Office Action

#### A. Restriction

The PTO finally withdrew claims 17 and 18 (Group II) from examination on the merits on the alleged basis that the technical feature of claims 10, 12-16 and 19 (Group I) differs from that of the Group II.

The amendments to claim 17, which now depends upon claim 10, should obviate the grounds for the PTO maintaining the restriction based on the unity of invention standard. Groups I and II, as framed by the PTO, require the administration of a specified glucuronidase inhibitor to a subject suffering from a condition that is characterized by high human tissue

glucuronidase activity. Claims 17 and 18, as with claims 15 and 16 (of Group I), merely provide for the administration of further components, but do not otherwise modify the special technical feature that is common to all of the claims within the meaning of PCT Rule 13. Accordingly, all of the claims should be examined together as one invention. Applicants therefore respectfully request the PTO to reconsider its withdrawal from examination of claims 17 and 18.

### B. Rejection Under 35 U.S.C. § 112, First Paragraph

The PTO rejected claim 15 under 35 U.S.C. § 112, first paragraph, for alleged want of written description for the recited combination of (1) a glucuronidase inhibitor, (2) a pharmacologically compatible adjuvant, and (3) a glucuronide conjugate of an inflammation-inhibiting active material. Applicants respectfully traverse this ground for rejection.

The amendments to the claims and specification should obviate this rejection. Specifically, original dependent claims 4 and 7 provide for the use of (1), (2), and (3). Accordingly, Applicants have amended the specification to incorporate such explicit support for the subject matter of claim 15. Claim 15, as amended, is directed to the use of (1) and (3). Consequently, this rejection is now moot, and Applicants respectfully request the PTO to reconsider and withdraw the rejection.

### C. Rejection of Claims Under 35 U.S.C. § 102

#### 1. Lehnert

Claims 10, 12-14, and 19 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Lehnert et al. ("Lehnert"). In support of the rejection, the PTO alleges that Lehnert teaches the administration of dexverapamil in combination with epirubicin for the treatment of breast cancer. Although Lehnert does not teach the claimed use of *R*-verapamil or a derivative thereof, the PTO deemed the use to be an inherent teaching of the reference, particularly in view of Applicants' "disclosing" the same ultimate purpose as that taught by Lehnert. Applicants respectfully traverse this ground for rejection.

Lehnert does not anticipate the claimed invention because the reference does not teach nor does it enable the claimed method. "A claim is anticipated only if each and every element as set forth in the claim i found, either expressly or inherently described, in a single prior art reference." MPEP §§ 2121 and 2131. Lehnert is directed to the reduction of multi-drug resistance attributed to an enhanced efflux of the administered drug from tumor cells. The desired effect of the disclosed combination treatment is the inhibition of P-glucoprotein.

By contrast, the claimed method addresses the treatment of a subject that is suffering from a condition that is characterized by high human tissue glucuronidase activity. Lehnert simply does not disclose this method. First, Lehnert does not teach the administration of a glucuronidase inhibitor, as claimed, to assist tumor therapy, as disclosed by the reference.

Second, as noted by the PTO, Applicants acknowledged that one effect of administering R-verapamil is that disclosed by Lehnert. *See* specification at page 5, lines 28 to page 6, line 12. Thus Lehnert can be viewed, at best, as disclosing a beneficial side effect resulting from performing the claimed method. But this falls short of the standard required for a reference to anticipate. Lehnert does not teach nor does it enable a person of skill in the art to administer a verapamil derivative to treat a subject that is suffering from a condition that is characterized by high human tissue glucuronidase activity. Since Lehnert fails to meet these criteria, it does not anticipate. Accordingly, Applicants respectfully request the PTO to reconsider and withdraw this ground for rejection.

**2. Scheithauer**

Claim 15 stands rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Scheithauer et al. ("Scheithauer"). The PTO evidently relied upon the reference for the purported disclosure of the claimed use of a glucuronidase inhibitor and a glucuronide conjugate of an inflammation-inhibiting active material.

Scheithauer, as with Lehnert discussed above, simply does not teach or enable the claimed method. In this case, Scheithauer is directed to the administration of dexverapamil, epirubicin, and GM-CSF for the treatment of a cancer. This does not teach or suggest that *R*-verapamil or a derivative thereof can be used to treat a condition that is characterized by

high human tissue glucuronidase activity. Consequently, Scheithauer does not anticipate. Applicants therefore respectfully request the PTO to reconsider and withdraw the rejection.

**3. Ratain**

Claims 10, 12-14, 16, and 19 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by U.S. Pat. No. 5,786,344 to Ratain et al. ("Ratain"). In support of this rejection, the PTO points out that Ratain teaches a method of reducing the toxicity of a camptothecin compound by the co-administration of that compound in combination with dexverapamil. As with the other cited references discussed above, the PTO deemed Ratain to inherently teach the claimed method even though the reference is silent as to the recited condition. Applicants respectfully traverse this ground for rejection.

Ratain teaches dexverapamil as useful for decreasing p-glycoprotein activity. Ratain at col. 9, lines 54-57. Additionally, Ratain teaches that an effect of the disclosed method is the *activation* of *glucuronosyltransferase*. *See id.* at col. 2, lines 61-67.

Ratain fails to teach or suggest the claimed method of administering a glucuronidase inhibitor for the treatment of a subject that is suffering from a condition that is characterized by high human tissue glucuronidase activity. Indeed, as noted above, the reference describes the activation of glucuronosyltransferase rather than inhibition of glucuronidase as claimed. Thus, while the disclosed verapamil undoubtedly possesses the recited activity, nowhere does the reference suggest the presence of this activity, much less that knowing this might enable one of skill in the art to practice the claimed method. Consequently, Ratain does not anticipate the claimed subject matter. Applicants therefore respectfully request the PTO to reconsider and withdraw this ground for rejection.

**C. Rejection Under 35 U.S.C. § 103**

Claim 19 was rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Jouvin-Marche et al. ("Jouvin-Marche"). The PTO pointed out that Jouvin-Marche teaches the use of a $Ca^{2+}$ antagonist, namely nifedipine, to inhibit $\beta$-glucuronidase. The PTO acknowledged that Jouvin-Marche does not teach the use of verapamil or its *R* enantiomer for

inhibiting β-glucuronidase, but the reference does mention verapamil as a $Ca^{2+}$ antagonist. Thus, the PTO reasoned first that a person of ordinary skill in the art would have concluded that inhibition of β-glucuronidase is "closely related" to inhibition of $Ca^{2+}$ uptake, and by this close relation that verapamil, as with nifedipine, could have been used to inhibit β-glucuronidase. Second, the PTO considered the recited *R* enantiomer to be obvious over the disclosed racemic verapamil. Applicants respectfully traverse the rejection.

Jouvin-Marche does not support the assumptions underlying the rejection for two reasons. First, a person of ordinary skill in the art would reject the notion that verapamil *per se* is useful for inhibiting $Ca^{2+}$ uptake. The art widely recognizes that *S*-verapamil is useful as a calcium antagonist, whereas the *R* enantiomer exhibits virtually no activity in this context whatsoever. *See* specification at page 5, lines 18-24 and references cited therein. Consequently, Jouvin-Marche *teaches away* from the claimed invention because the person of ordinary skill in the art would know that the reference refers to *S*-verapamil as the calcium uptake inhibitor.

Second, Jouvin-Marche does not teach or suggest the close relationship posited by the PTO, i.e., that $Ca^{2+}$ antagonists will also give rise to the inhibition of β-glucuronidase. Moreover, the reference is silent as to whether verapamil, much less *R*-verapamil, engenders such a relationship. In any event, as noted above, *R*-verapamil shows little to no $Ca^{2+}$ antagonist activity and is therefore incomparable to nifedipine for this reason. Consequently, Jouvin-Marche undermines the logic of the rejection: the PTO stated that, on one hand, an exchange of nifedipine by verapamil is obvious because of their common activity as $Ca^{2+}$ antagonists, but considered, on the other hand, the selection of *R*-verapamil over racemic verapamil also as obvious even though it is known that *R*-verapamil is not a $Ca^{2+}$ antagonist.

The PTO relies to no avail upon Sim et al. and Hashimoto et al. to establish the "close relationship" between $Ca^{2+}$ antagonism and β-glucuronidase inhibition for a drug that is known to exhibit one. Both references would only suggest the use of *S*-verapamil or, at best, the racemic mixture. In fact, Hashimoto does not mention verapamil at all, while Sim states that the effect of verapamil was only slight. In any event, neither reference remotely ascribes $Ca^{2+}$ antagonism to *R*-verapamil.

For the foregoing reasons, a person of ordinary skill in the art would not have considered the claimed invention to have been obvious over Jouvin-Marche. Applicants therefore courteously request the PTO to reconsider and withdraw this ground for rejection.

## IV. Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if he feels that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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**The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.**